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SPECIAL FEATURE

A Review of Current Therapeutics for Severe COVID-19 Pneumonia

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Dr. Shah reports that he has received a clinical trial grant from Actelion Pharmaceuticals/Janssen Research, Bayer Pharmaceuticals, United Therapeutics Corporation, Liquidia Technologies, Medtronic Inc., and Regeneron Pharmaceuticals. He serves as a consultant for Bayer. He also has served as site principal investigator for UT Southwestern for the Regeneron monoclonal antibody trial.

Since the first reported case on Nov. 17, 2019, in Hubei Province, China, COVID-19 has spread across the world as the most dreadful pandemic in modern history. It has been more than a year since the onset of this pandemic, and multiple therapeutic options have been considered for COVID-19 pneumonia across the world. The aim of this special feature is to review therapeutic options for hospitalized patients with COVID-19 pneumonia.

Current COVID-19-specific therapeutics target viral replication, inflammation, and hypercoagulability. It must be noted that for most of these therapeutics, except perhaps corticosteroids, data are low quality. COVID-19-related hypercoagulability is a separate topic, and current trials are ongoing, with most places using modified protocols for hospitalized patients based on severity of illness, laboratory values, and other clinical parameters. It is safe to say that all hospitalized patients with COVID-19 should receive pharmacological prophylaxis for venous thromboembolism, and consideration should be given to therapeutic anticoagulation in select patients. The therapeutics discussed in this review are summarized in Table 1.

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THERAPEUTICS THAT TARGET INFLAMMATION

Corticosteroids

Prior to the COVID-19 pandemic, previous studies of corticosteroids in Middle East respiratory syndrome (MERS)-CoV, severe acute respiratory syndrome (SARS)-CoV-1, and influenza virus infections have been largely negative, showing increased mortality, secondary infections, adverse effects, and impaired viral clearance.[1-3] In addition, trials on the use of steroids in acute respiratory distress syndrome (ARDS) have shown increased mortality if given after two weeks and no mortality benefit even if given in the first two weeks.[4] Therefore, in routine clinical practice, corticosteroids are not commonly used for ARDS in the absence of another compelling indication.

In contrast, multiple trials in severe COVID-19 pneumonia and ARDS suggest a mortality benefit with steroids. The largest of these is the Randomized Evaluation of COVID-19 Therapy (RECOVERY) trial, which showed significant improvement in 28-day mortality in patients who received dexamethasone 6 mg daily for 10 days vs. usual care (22.9 % vs. 25.7%, respectively; odds ratio [OR] 0.83; 95% confidence interval [CI], 0.75-0.93).[5] This difference was more striking in patients who were receiving invasive mechanical ventilation (29.3% for dexamethasone vs. 41.4% for usual care; OR, 0.64; 95% CI, 0.51-0.81) and receiving supplemental oxygen (23.3% for dexamethasone vs. 26.2% for usual care; OR, 0.82; 95% CI, 0.72-0.94), but there was no significant difference between groups in patients not receiving respiratory support at randomization (17.8% vs. 14%; OR, 1.19; 95% CI, 0.91-1.55). Also, dexamethasone decreased the length of hospitalization and increased the probability of being discharged alive at 28 days, with the greatest effect in mechanically ventilated patients.

The World Health Organization (WHO) Rapid Evidence Appraisal for COVID-19 Therapies (REACT) working group conducted a meta-analysis of seven randomized controlled trials (RCTs) in critically ill patients (three trials with dexamethasone, three with hydrocortisone, and one with methylprednisolone), which showed a significant improvement in 28-day mortality with steroids (OR, 0.66; 95% CI, 0.53-0.82).[6] It should be noted that this meta-analysis included the RECOVERY trial. Based on these data, it is safe to extrapolate that treatment with corticosteroids (dexamethasone 6 mg daily × 10 days or equivalent) is beneficial in COVID-19 pneumonia and ARDS.

Anti-IL-6, Anti-IL-1 Agents and Janus Kinase Inhibitors

Because of initial reports of cytokine storm associated with COVID-19 infection, immunosuppressive therapies have been explored, especially in critically ill patients. These were triggered by initial case series from China that suggested that tocilizumab (anti-interleukin-6 [anti-IL-6]) not only improved oxygenation and fever curve, but that all patients were discharged alive after receiving tocilizumab.[7] Other anecdotal and observational studies seemed to show a benefit with tocilizumab as well in patients with cytokine storm. However, two randomized trials with sarilumab failed to achieve their primary endpoints. In press releases, Regeneron and Sanofi indicated minor positive trends in patients receiving mechanical ventilation at baseline, but these did not achieve statistical significance, and the results, unfortunately, are not published.

Italian and French groups have given retrospective reports of benefit using anakinra (anti-interleukin-1 [anti-IL-1]).[8,9] Baricitinib, a Janus kinase (JAK) inhibitor, was evaluated in the Adaptive COVID-19 Treatment Trial (ACTT)-2 study conducted by the National Institute of Allergy and Infectious Diseases (NIAID). In this study, baricitinib plus remdesivir decreased the median time to recovery and odds of progressing to death or mechanical ventilation by day 29 as compared to remdesivir alone. It also improved the odds of clinical improvement at day 15. The baricitinib group had increased serious adverse events, with increased risk of venous thromboembolism and serious infections. The Food and Drug Administration (FDA) recently granted emergency use authorization (EUA) to the baricitinib plus remdesivir combination and

Table 1: Current COVID-19 Therapeutics

Treatment	Benefit	Quality of Evidence	Recommended Dose	Comments
Corticosteroids	Yes	Good: large RCT and one meta-analysis	Dexamethasone 6 mg/day x 10 days	Equivalent doses of other corticosteroids are acceptable
Anti-IL-6 agents (tocilizumab, sarilumab)	Not likely	Sarilumab: good; two RCTs Tocilizumab: poor; observational studies	Sarilumab: dose not established Tocilizumab: 400 mg IV (off label)	Could consider tocilizumab in select patients with cytokine storm. Data on such use are limited to observational studies.
Janus kinase inhibitors (baricitinib)	Probable in combination with remdesivir	Fair: one RCT with mild treatment effect	Baricitinib: 4 mg/day for 14 days or until hospital discharge	Increased venous thrombosis and infections associated with baricitinib
Remdesivir	Possible	Good: two large RCTs with conflicting results	200 mg IV once followed by 100 mg daily x 4 days (total five days)	Accumulates in renal failure and monitor for hepatotoxicity. Likely benefit in patients on low-flow oxygen.
Convalescent plasma	Not likely	Fair: one RCT without benefit and the other RCT was underpowered	Varies in different studies: most commonly 1-2 units	If used, consider early in course of disease
Neutralizing monoclonal antibodies (bamlanivimab, casirivimab + imdevimab cocktail)	Not definitely known	Two RCTs showed benefit in outpatient setting. No published data for inpatients yet.	Bamanivimab: 700 mg IV over 60 minutes; Casirivimab 1,200 mg + imdevimab 1,200 mg once over 60 minutes	Provides passive immunity and likely could benefit early in course of disease. Further RCT data are awaited; currently not recommended to be used outside of clinical trial in inpatient setting
Hydroxychloroquine	No	Good: three large RCTs did not show benefit	Not recommended	FDA withdrew EUA for hydroxychloroquine

RCT: randomized controlled trial; IV: intravenous; FDA: Food and Drug Administration; EUA: emergency use authorization

cautions against use of baricitinib alone. Currently, peer-reviewed publication is awaited.

COVID-19-SPECIFIC THERAPEUTICS

Remdesivir

Remdesivir is the first FDA-approved medication for COVID-19 viral infection. Data to support its use come from ACTT-1 and two other smaller randomized controlled trials.[10-12] The ACTT-1 trial was performed by NIAID on 1,062 patients with evidence of lower respiratory tract infection. Of these, 541 patients were assigned to the remdesivir arm and 520 to the placebo arm. Patients in the remdesivir arm had a median recovery time of 10 days as opposed to 15 days for placebo and were more likely to have clinical improvement at day 15. Overall, 28-day mortality was lower at 11.4% with remdesivir as compared to 15.2% with placebo, but this did not reach statistical significance. In a subgroup analysis, remdesivir decreased 28-day mortality in patients on low-flow oxygen (relative risk [RR] 0.3; 95% CI, 0.11-0.81) but not in patients on high-flow oxygen, noninvasive ventilation, mechanical ventilation, or no oxygen.[12] However, in the much larger SOLIDARITY trial by WHO across 30 countries, remdesivir did not lead to significant improvement in 28-day mortality as compared to placebo (RR 0.95; 95% CI, 0.81-1.11, $P = 0.50$).[13] Currently, we still are waiting for peer-reviewed publication of these results. It should be noted that WHO no longer recommends remdesivir based on a meta-analysis that included pre-print results of the WHO SOLIDARITY trial.[14] Despite this, in most hospitals across the United States, remdesivir still is included as treatment for patients with severe COVID-19 pneumonia and ARDS. If remdesivir is used, a five-day course is equivalent to a 10-day course.[10] In all trials, there was no benefit of remdesivir in patients receiving mechanical ventilation or on extracorporeal membrane oxygenation (ECMO), and it is not recommended in these populations.

Convalescent Plasma

Since the onset of the COVID-19 pandemic, convalescent plasma was considered a potential treatment based on experience with other coronavirus (SARS-CoV-1 and MERS) and influenza (H1N1, H5N1) viral infections. A meta-analysis of 32 such studies showed decreased mortality with convalescent

plasma.[15] Thus far for COVID-19 infection, data on the use of convalescent plasma have been limited, and based on current evidence, its use is at best experimental. However, the FDA has issued an EUA for the use of convalescent plasma. To date, two randomized controlled trials of convalescent plasma did not show statistically significant benefits in mortality or clinical improvement.[16,17] The Mayo Clinic has published their experience in 20,000 patients with COVID-19 who received convalescent plasma through their expanded access program. They reported a low risk of serious adverse events and seven-day mortality of 8.6% (95% CI, 8.2% to 9.0%).[18]

Neutralizing Monoclonal Antibodies

In an attempt to confer passive immunity like convalescent plasma, monoclonal antibodies have been developed against the spike protein of SARS-CoV-2. Recently, the FDA issued an EUA to bamlanivimab (made by Eli Lilly) and the casirivimab plus imdevimab cocktail (made by Regeneron) for outpatient use only.[19] Both monoclonal antibodies were well tolerated without significant serious adverse events. Currently, randomized controlled trials of these monoclonal antibodies are ongoing for inpatients, and further data are awaited.

OTHER THERAPEUTICS

Hydroxychloroquine

Initially in the COVID-19 pandemic, hydroxychloroquine was used extensively based on observational studies and it even received an EUA by the FDA. However, multiple large, randomized controlled trials, including the RECOVERY, SOLIDARITY, and ORCHID trials, did not show benefit. Peer-reviewed published data for these trials are awaited, but currently there are strong data against the use of hydroxychloroquine in COVID-19 infection. The FDA revoked its EUA for hydroxychloroquine on June 15, 2020.

Favipiravir, Lopinavir/Ritonavir, Interferons, Azithromycin, and Ivermectin

None of these agents are recommended for use outside of clinical trials. There is a significant amount of published literature that does not show benefit for azithromycin, lopinavir/ritonavir, interferons, and ivermectin. Two trials from China and one from Russia with favipiravir showed improved viral clearance, higher clinical recovery, and radiographic improvement. However, it is difficult to conclude efficacy because of limitations in these trials, and the patients included were on other therapies for COVID-19.

CONCLUSION

Many therapeutic options are being considered for the management of COVID-19 infection. At the current time, data strongly suggest the use of corticosteroids in patients with severe COVID-19 pneumonia and ARDS with significant mortality benefit. Remdesivir shortens time to recovery and clinical improvement in patients with severe COVID-19 pneumonia, but not in patients on mechanical ventilation or ECMO, and it has not shown mortality benefit. Baricitinib, when added to remdesivir, showed some further benefit in expediting clinical improvement, but did not impact mortality. Multiple other agents are undergoing ongoing investigation to assess for clinical benefit, and several other agents that showed initial promise are no longer being used due to lack of benefit. ■

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ABSTRACT & COMMENTARY

Convalescent Plasma Therapy Does Not Affect Time to Clinical Improvement in Patients with Severe and Life-Threatening COVID-19

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Dr. Sharma reports no financial relationships relevant to this field of study.

SYNOPSIS: This was a randomized, open-label, multicenter trial of intravenous convalescent plasma infusion (4 mL/kg to 13 mL/kg) therapy. Convalescent plasma therapy was not associated with improvements in mortality or time to clinical improvement.

SOURCE: Li L, Zhang W, Hu Y, et al. Effect of convalescent plasma therapy on time to clinical improvement in patients with severe and life-threatening COVID-19: A randomized clinical trial. *JAMA* 2020;324:460-470.

This was an open-label, multicenter, randomized trial conducted in Wuhan, China, that started recruiting patients in February 2020. Patients with laboratory-confirmed COVID-19 infection with severe (defined as respiratory distress or hypoxemia) or life-threatening (mechanical ventilation, shock, or organ failure) disease were recruited. Patients with contraindications to plasma infusion, severe septic shock, $PaO_2/FiO_2 < 100$, severe congestive heart failure, immunoglobulin A (IgA) deficiency, and those who were pregnant/lactating were excluded. Additionally, patients with a positive antibody test to COVID-19 also were excluded. The trial enrolled 103 patients and had to be terminated prematurely in April 2020 at 50% of target recruitment because of a lack of patients with COVID-19.

Convalescent plasma (CVP) was collected from donors with prior COVID-19 infection with two negative nasopharyngeal polymerase chain reaction (PCR) tests. COVID-19 S-protein-receptor binding domain-specific immunoglobulin G (IgG) antibody levels were measured in the specimens, and only those units with a titer of at least 1:640 were used in the study. The volume of plasma transfused was 4 mL/kg to 13 mL/kg of actual patient body weight. Plasma was infused with usual precautions for transfusion-related reactions. The majority of those enrolled (101/103, 98%) were included in the per-protocol analysis.

The primary outcome was clinical improvement within a 28-day period after randomization. Multiple secondary outcomes were assessed, including 28-day mortality, duration of hospitalization, and proportion of nasopharyngeal swab conversion to negative. A post-hoc analysis was added to assess rates of improvement at one and two weeks as well. A six-point disease severity scale was used to assess clinical improvement (described as a two-point or greater reduction in the disease severity scale). The scale awarded points according to disease severity: death (6 points), extracorporeal membrane oxygenation (ECMO) or invasive mechanical ventilation (5 points), noninvasive ventilation or high-flow oxygen (4 points), nasal cannula oxygen (3 points), hospitalization (2 points), and discharge from the hospital (1 point). This

scale was adapted from and has been used previously in patients studied in an influenza-related plasma infusion trial.[1]

For all patients, no differences were found in the primary outcome. More importantly, for those with severe disease, the primary outcome (two-point improvement in severity score) occurred in 20.7% who received CVP, and 24% in those who did not ($P = 0.83$). Secondary clinical outcomes were no different between groups except that those individuals receiving CVP had a higher rate of nasopharyngeal PCR conversion to negative at 24-72 hours. Two transfusion-related adverse effects were observed with the use of CVP: One patient developed a rash and another developed severe dyspnea six hours after transfusion of plasma.

■ COMMENTARY

This study concludes that CVP therapy does not affect relevant outcomes among hospitalized patients with COVID-19 infection. The rates of death were equivalent among groups. Although a higher proportion of patients receiving CVP therapy converted nasopharyngeal swabs to negative, the clinical relevance of this finding is not clear.

Several limitations deserve to be highlighted. First, the study was underpowered for the primary outcome because of a small number of patients enrolled. Second, the median time between onset of symptoms and randomization was 30 days. Studies published after this trial was published suggest a benefit for infusion of monoclonal antibodies early (as early as outpatient status) in the course of illness.[2] Another assessed transfusion of CVP with high titer of anti-spike protein receptor binding domain antibodies (≥ 1:1350) and found a significant reduction in 28-day mortality when transfused within 72 hours of admission.[3] Third, standard therapy for severe COVID-19 infection was used in all patients but was not protocolized. Most importantly, the group that was randomized to receive CVP had a higher proportion of patients receiving steroids (46% vs. 33%, respectively), and dexamethasone has been shown to reduce mortality in COVID-19 patients.[4] Finally, although the inclusion criterion was "severe or life-threatening COVID-19 infection," 32/103 (31%) of patients randomized had a disease severity score of 2 or 3 and were either not on oxygen or were on supplemental oxygen alone (not high-flow or noninvasive ventilation). The definition of severe disease was a respiratory rate of ≥ 30/minute at rest, an O_2 saturation of 93% or less on room air, or a $PaO_2/FiO_2 < 300$; debatably, these are a broad set of descriptors. CVP therapy is safe for the most part, with one patient developing a severe transfusion reaction in this study. A larger study of 20,000 patients had similar findings, with a rate of transfusion reactions of < 1%.[5] In the study reviewed here, patients with $PaO_2/FiO_2 < 100$ were excluded, so there remains the concern that a severe transfusion reaction in this group may be fatal.

In conclusion, based on the results of this study, CVP therapy is unlikely to be of benefit late in the course of the disease, and CVP with higher titer antibodies may be more effective. Enrolling patients early in a high-titer antibody plasma infusion trial remains the most plausible recommendation currently. Further data should be forthcoming given ongoing trials (NCT04372979, NCT04513158, NCT04412846). ■

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ABSTRACT & COMMENTARY

Patients with Higher Renin Levels May Derive More Benefit from Angiotensin II Treatment

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Dr. Tran reports no financial relationships relevant to this field of study.

SYNOPSIS: Serum renin concentration in patients with catecholamine-resistant vasodilatory shock may identify those for whom treatment with angiotensin II has improved intensive care unit outcomes.

SOURCE: Bellomo R, Forni LG, Busse LW, et al. Renin and survival in patients given angiotensin II for catecholamine-resistant vasodilatory shock. *Am J Respir Crit Care Med* 2020;202:1253-1261.

The renin-angiotensin-aldosterone (RAAS) system plays an important role in regulating blood pressure. Renin, an enzyme secreted by the kidneys in response to sympathetic nerve activation, hypotension, or decreased sodium delivery to the distal tubule, cleaves angiotensinogen to angiotensin I. Angiotensin I then is cleaved by angiotensin-converting enzyme (ACE), an endothelial membrane-bound enzyme, to angiotensin II. Angiotensin II functions through a myriad of effects, including acting on the adrenal cortex to release aldosterone to increase sodium and fluid retention to elevate systemic vascular resistance and arterial pressure.

Physiologically, the premise for this study is based on the idea that endothelial injury seen in catecholamine-resistant vasodilatory shock (CRVS) leads to a decrease in ACE function, thereby increasing angiotensin I/II ratios and promoting high renin levels. Patients with high renin levels, therefore, may be a population most likely to benefit from treatment with angiotensin II.

This was a post hoc analysis of the Angiotensin II for the Treatment of High-Output Shock 3 (ATHOS-3)[1] study, which enrolled adults with vasodilatory shock despite volume resuscitation with > 25 mL/kg and high-dose vasopressors (norepinephrine equivalent dose > 0.2 µg/kg/min). Participants were randomized 1:1 to receive saline placebo or angiotensin II, with the study drug started at 20 ng/kg/min adjusted during the first three hours to increase mean arterial pressure (MAP) to > 75 mmHg. Bellomo and colleagues obtained serum renal levels for 255 (79.4%) patients who participated in the original study. The median serum renin concentration was 172.7 pg/mL: (interquartile range [IQR] 60.7 pg/mL to 440.6 pg/mL), which was three-fold higher than the upper limit of normal. Renin levels positively correlated to angiotensin I/II ratios and angiotensin I levels. After three hours, patients treated with angiotensin II had significant reductions in renin and angiotensin I levels compared to placebo.

Patients were dichotomized by median serum renin concentration (i.e., above median renin and below median renin), with good balance between the placebo and angiotensin II treatment groups within these subpopulations. In a multivariable analysis, in patients with a renin concentration above the median, treatment with angiotensin II was associated with a decreased risk of mortality at 28 days (hazard ratio [HR] 0.62; 95% confidence interval [CI], 0.39–0.98, $P = 0.0423$). In contrast, there was no significant difference in mortality for those with serum renin concentrations below the median. Similarly, for the subset of patients with renin concentrations above the median, the rate of renal replacement therapy (RRT) liberation by day 7 was significantly higher in patients treated with angiotensin II compared to placebo (43% vs. 12%, $P = 0.01$), as was the rate of intensive care unit (ICU) discharge by day 28 (44% vs. 22%, respectively, $P = 0.02$). There were no differences in these outcomes between treatment groups in patients with renin concentrations below the median. The rate of ventilator liberation at day 7 did not differ significantly between treatment groups in either of the subpopulations.

■ COMMENTARY

When the results of ATHOS-3 first were published,[1] it was encouraging to see positive results from a new class of vasopressor. However, several questions remained regarding its use: Is angiotensin II better than other agents already in use (e.g., norepinephrine, vasopressin, etc.)? Aside from raising MAP, are there more compelling outcomes associated with its use? Which patients are the best candidates to derive benefit from it?

Bellomo and colleagues attempted to address this last question. This study's biggest strength and, arguably, impact is its consistency with known mechanisms and physiology related to the renin-angiotensin-aldosterone system. The investigators were able to show that renin levels positively correlated with baseline angiotensin I and angiotensin I/II ratios, the latter of which can be used as a surrogate for ACE activity. Consistent with prior findings,[2] elevated renin levels were independently associated with an increased risk of death. In patients with elevated renin levels above the study median (172.7 pg/mL), treatment with synthetic angiotensin II was associated not only with lower renin levels after three hours, but also decreased 28-day mortality, liberation or freedom from RRT at day 7, and ICU discharge by day 28.

It is interesting to note that the MAP response in patients treated with angiotensin II vs. placebo was not affected by baseline renin level. In other words, even patients with renin concentrations below the study median had a MAP response to angiotensin II, despite not having improved outcomes. As such, the authors suggested that elevated renin levels may have other

deleterious effects that may modify the effect by treatment group independent of MAP. For example, renin may activate receptors on leukocytes, resulting in the production of pro-inflammatory cytokines; the use of angiotensin II, by reducing renin levels, may modulate the inflammatory response and thereby improve survival. In addition, normalization of renin levels with angiotensin II may activate angiotensin II receptors in end organs, such as the kidneys, thereby increasing glomerular filtration rate and urine output and enhancing renal recovery.

This study has several notable limitations when evaluating their findings. First, the post hoc analysis requires validation in a prospective trial. Second, the finding that the effect of modification of renin on the treatment group was only present when renin was treated as a dichotomous variable (i.e., above or below the study median) as opposed to a continuous variable is arbitrary and should not be viewed as a physiologically meaningful cutoff. Third, the original ATHOS-3 trial was not stratified at baseline by renin level; therefore, differences in outcomes between the angiotensin II and placebo treatment groups in the subgroup of patients with higher renin level may be the result of chance imbalances in baseline characteristics.

Nevertheless, this study represents a strong start to defining how treatment effects can be heterogeneous, which patients may benefit the most from angiotensin II, and ultimately, how we can make more personalized, evidence-based decisions for our patients. ■

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CME/CE QUESTIONS

1. **For a hypoxic patient with COVID-19 pneumonia, which medication should be considered based on the current evidence in the literature?**
   a. Bamlanivimab 700 mg intravenous (IV) once over 60 minutes
   b. Hydroxychloroquine
   c. Dexamethasone 6 mg daily for 10 days
   d. Tocilizumab
2. **Which of the following medications is Food and Drug Administration-approved for use in patients with COVID-19 pneumonia?**
   a. Hydroxychloroquine
   b. Bamlanivimab
   c. Convalescent plasma
   d. Remdesivir
3. **Which of the following was used to define life-threatening COVID-19 infection in the convalescent plasma trial?**
   a. Use of high-flow nasal cannula oxygen therapy
   b. O_2 saturation < 93%
   c. Organ failure requiring intensive care unit (ICU) monitoring
   d. PaO_2/FiO_2 < 300
4. **Which of the following was a contraindication to infusion of convalescent plasma?**
   a. PaO_2/FiO_2 < 300
   b. PaO_2/FiO_2 < 200
   c. PaO_2/FiO_2 < 100
   d. Any PaO_2/FiO_2 and need for positive end-expiratory pressure > 15
5. **In the study by Bellomo et al, high serum renin levels:**
   a. correlated positively with angiotensin I/II ratios.
   b. correlated positively with angiotensin II levels.
   c. did not change despite treatment with synthetic angiotensin II.
   d. were seen rarely in the study population.
6. **In the study by Bellomo et al, treatment with angiotensin II was associated with:**
   a. higher rates of ventilator liberation at day 7 regardless of renin level.
   b. higher rates of liberation from renal replacement therapy at day 7 regardless of renin level.
   c. reduced mortality in patients with renin concentrations above the study median.
   d. higher rates of ICU discharge at day 28 in patients with renin concentrations below the study median.